Randomized, controlled clinical two-centre study using xenogeneic block grafts loaded with recombinant human bone morphogenetic protein-2 or autogenous bone blocks for lateral ridge augmentation

Thoma, Daniel S ; Payer, Michael ; Jakse, Norbert ; Bienz, Stefan P ; Hüsler, Jürg ; Schmidlin, Patrick R ; Jung, Ui-Won ; Hämmerle, Christoph H F ; Jung, Ronald E

Abstract: OBJECTIVES To test whether or not the use of a xenogeneic block loaded with recombinant human bone morphogenetic protein-2 (rhBMP-2) results in different bone quantity and quality compared to an autogenous bone block. MATERIALS AND METHODS Twenty-four patients with insufficient bone volume for implant placement were randomly assigned to two treatment modalities: a xenogeneic bone block loaded with rhBMP-2 (test) and an autogenous bone block (control). The horizontal ridge width was evaluated prior to augmentation, after augmentation and at 4 months. Patient-reported outcome measures (PROMs) were assessed at suture removal and at 4 months. Biopsies were obtained at 4 months and histologically evaluated. Intergroup comparisons were tested by a two-sided Wilcoxon-Mann-Whitney test, intra-group comparisons were performed with Wilcoxon-signed rank test, and all categorical variables were tested with Chi-squared tests. RESULTS One autogenous bone block failed. This patient was replaced, and in all subsequently treated 24 patients, implant placement was possible 4 months later. The median ridge width increased from 4.0 mm (Q1 = 2.0; Q3 = 4.0) (test) and 2.0 mm (Q1 = 2.0; Q3 = 3.0) (control) to 7.0 mm (Q1 = 6.0; Q3 = 8.0) (test) and 7.0 mm (Q1 = 6.0; Q3 = 8.0) (control) at 4 months (intergroup $p > .05$). A higher morbidity was reported at the augmented site in the control group during surgery. Sensitivity was more favourable in the test than that in the control group at 4 months. The biopsies revealed more mineralized tissue in the control group ($p < .0043$). CONCLUSIONS Both treatment modalities were successful in regenerating bone to place dental implants. PROMs did not reveal any significant differences between the groups except for pain during surgery at the recipient site (in favour of the test group). Histologically, a higher amount of mineralized tissue was observed for the control group at 4 months.

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Daniel S. Thoma[1*], Michael Payer[2*], Norbert Jakse[2], Stefan P. Bienz[1], Jürg Hüsler[1], Patrick R. Schmidlin[3], Ui-Won Jung[4], Christoph H.F. Hämmerle[1], Ronald E. Jung[1]

*these authors contributed equally to the study

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Address for correspondence:
PD Dr. Daniel S. Thoma
Clinic of Fixed and Removable Prosthodontics and Dental Material Science
Center of Dental Medicine, University of Zurich
Plattenstrasse 11
CH-8032 Zurich, Switzerland
Phone: +41 44 634 42 56
Fax: +41 44 634 43 05
e-mail: daniel.thoma@zzm.uzh.ch

[1] Clinic for Fixed and Removable Prosthodontics and Dental Material Science, University of Zurich, Zurich, Switzerland

[2] Department of Oral Surgery and Radiology, School of Dentistry, Medical University Graz, Graz, Austria

[3] Clinic of Preventive Dentistry, Periodontology and Cariology, Center of Dental Medicine, University of Zurich, Zurich, Switzerland

[4] Department of Periodontology, Research Institute for Periodontal Regeneration, Yonsei University College of Dentistry, Seoul, Korea

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Abstract

Objectives: to test whether or not the use of a xenogeneic block loaded with recombinant human bone morphogenetic protein-2 (rhBMP-2) results in different bone quantity and quality compared to an autogenous bone block.

Materials and methods: 24 patients with insufficient bone volume for implant placement were randomly assigned to two treatment modalities: a xenogeneic bone block loaded with rhBMP-2 (test) or an autogenous bone block (control). The horizontal ridge width was evaluated prior to augmentation, after augmentation and at 4 months. Patient-reported outcome measures (PROMs) were assessed at suture removal and at 4 months. Biopsies were obtained at 4 months and histologically evaluated. Intergroup comparisons were tested by a two-sided Wilcoxon-Mann-Whitney test, intragroup comparisons were performed with Wilcoxon-signed rank test and all categorical variables were tested with chi-square tests.

Results: One autogenous bone block failed. This patient was replaced and in all subsequently treated 24 patients, implant placement was possible 4 months later. The median ridge width increased from 4.0 mm (Q1 = 2.0; Q3 = 4.0) (test) and 2.0 mm (Q1 = 2.0; Q3 = 3.0) (control) to 7.0 mm (Q1 = 6.0; Q3 = 8.0) (test) and 7.0 mm (Q1 = 6.0; Q3 = 8.0) (control) at 4 months (intergroup $p>0.05$). A higher morbidity was reported at the augmented site in the control group during surgery. Sensitivity was more favorable in the test than in the control group at 4 months. The biopsies revealed more mineralized tissue in the control group ($p<0.0043$).

Conclusions: Both treatment modalities were successful in regenerating bone to place dental implants. PROMs did not reveal any significant differences between the groups except for pain during surgery at the recipient site (in favor of the test group). Histologically, a higher amount of mineralized tissue was observed for the control group at 4 months.

Clinical Relevance

Scientific rationale for the study: For primary bone augmentation, the use of autogenous block grafts is considered to be the gold standard for GBR. This approach is associated with an increased patient morbidity. In order to avoid this limitation, a form-stable xenogeneic block graft loaded with an osteoinductive growth factor (recombinant human bone morphogenetic protein-2 (rhBMP-2) was proposed as a treatment alternative.

Principal findings: Four months after ridge augmentation, implant placement was possible in all patients and the obtained ridge width was comparable in both groups. Patient-reported outcome measures did not reveal any significant differences between the groups except for pain during surgery at the recipient site (in favor of the test group). Histologically, a higher amount of mineralized tissue was observed for the control group at 4 months.

Practical implications: The combination of a xenogeneic block loaded with rhBMP-2 might be an alternative treatment option for lateral ridge augmentation, offering sufficient bone regeneration to place dental implants four months after primary augmentation.

Introduction

A variety of surgical techniques and biomaterials have been described in the literature to enhance deficient alveolar bone volume prior to implant placement: autogenous bone grafts, distraction osteogenesis, bone splitting and guided bone regeneration (GBR) (Buser et al., 1993, Cordaro et al., 2002, Oda et al., 2000, Milinkovic and Cordaro, 2014). Among these, GBR is one of the best documented methods reporting high success rates for bone regeneration (Hammerle and Karring, 1998, Hammerle and Jung, 2003) and implant survival rates in augmented bone (Nevins et al., 1998, Clementini et al., 2012).

Autogenous bone grafts are considered to be the gold standard for GBR using a staged approach with subsequent implant placement (Nevins and Mellonig, 1994, von Arx et al., 2001). The addition of deproteinized bovine bone mineral (DBBM) particles to cover the block and fill voids has shown to be effective in terms of clinical and histological results (Proussaefs and Lozada, 2003, Proussaefs et al., 2002, von Arx and Buser, 2006) and does further decrease the amount of resorption (Maiorana et al., 2005, Wiltfang et al., 2014, Cordaro et al., 2011). The use of a second surgical site is reported to be a major drawback when using autogenous bone blocks. Complications including altered sensation of teeth, neurosensory disturbances, wound dehiscence, and infections have been described (Nkenke et al., 2001, von Arx et al., 2005).

In order to overcome issues due to the harvesting procedure, research activities were directed towards the development of biomaterials. Clinical studies demonstrated that the use of a xenogeneic grafting material in combination with a collagen membrane was an effective treatment modality for staged horizontal bone augmentation (Hammerle et al., 2008, Norton et al., 2003). In addition, research has focused on the use of bioactive molecules to induce localized bone formation (Urist, 1965, Reddi et al., 1987). Among more than 30 identified bone morphogenetic proteins (BMP), only a small number (BMP-2, BMP-4, BMP-7, BMP-9) appeared to have osteoinductive functions (Cheng et al., 2003).

Various combinations of recombinant human bone morphogenetic protein-2 (rhBMP-2), the most potential growth factor, and carrier materials have been evaluated in the past (Jung et al., 2008, Schliephake, 2015). Early attempts used an absorbable collagen sponge to serve as a carrier for

rhBMP-2. This combination, however, failed to demonstrate adequate mechanical stability (Barboza et al., 2000). In a more recent preclinical study, rhBMP-2 was combined with a printed PCL/PLGA/β-TCP membrane. Statistically significantly more bone formation was found underneath membranes combined with rhBMP-2 (Shim et al., 2014). Clinically, xenogeneic bone substitute materials are frequently used for various guided bone regeneration procedures. The same materials were also used as carrier materials for biologic mediators, the first time in combination with rhBMP-7 (Terheyden et al., 1999). The intent, at that time, was to provide an osteoconductive carrier serving to provide mechanical stability and to induce cell infiltration. A randomized controlled clinical study demonstrated an enhanced process of bone regeneration and an increased graft to bone contact for rhBMP-2 combined with a xenogeneic bone substitute materials (Jung et al., 2003). Excellent radiological outcomes were reported during a 3- and 5-year follow-up (Jung et al., 2009).

Currently, no scientific data exist with respect to clinical studies comparing the gold standard (autogenous bone graft plus collagen membrane) with the promising combination of a xenogeneic bone graft loaded with rhBMP-2 for localized ridge augmentation.

The aim of the present study was therefore, to test whether or not, for primary bone augmentation, the use of a xenogeneic block loaded with rhBMP-2 results in different bone quantity (clinically) and quality (histologically) compared to an autogenous bone block and to evaluate patient morbidity following the surgical interventions with the two treatment modalities.

Materials and methods

The present two-center study was designed as an exploratory, prospective, randomized, controlled clinical trial. The local ethical committees of Zurich and Graz approved all procedures and materials prior to the start of the investigation. Informed consent was obtained from all participating patients. Twenty-four patients were scheduled to be included and to be consecutively treated at the Clinic for Fixed and Removable Prosthodontics and Dental Material Science, University of Zurich, Zurich, Switzerland (center 1) and at the Department of Oral Surgery and Radiology, School of Dentistry, Medical University Graz, Graz, Austria (center 2). The sample size of the present study was determined based on a previous clinical study using 11 patients in a split-mouth design using the same growth factor and xenogeneic bone substitute material (Jung et al., 2003). Since no clinical data were available for the same combination of materials for primary augmentation, the number of patients was increased to 24 (non-split-mouth design), but considered to be of exploratory nature.

Patients

A total of 24 partially edentulous patients in need of implant therapy and presenting an insufficient bone volume (horizontal ridge width <5mm) to allow placing a standard diameter implant defect-free in a prosthetically ideal position were included.

Specific exclusion criteria:

- pregnancy, intention to become pregnant, breast feeding, lack of safe contraception
- Medication with a contraindication for implant therapy
- Previous administration of InductOs®
- Skeletal immaturity
- Any active malignancy or patient undergoing treatment for a malignancy
- Persistent compartment syndrome or neurovascular residua of compartment syndrome
- Pathological fractures such as those observed in (but not limited to) Paget's disease or in metastatic bone

- Contraindications to the class of drugs under study, e.g. known hypersensitivity or allergy to class of drugs or the investigational product

Specific inclusion criteria:

- >18 years of age
- good general health and no systemic disease
- periodontally healthy (BOP and Pl <25%)
- smoking habit: <10 cigarettes per day
- partially edentulous and in need of implant therapy
- insufficient ridge width (<5mm) to place dental implants at 1-4 sites in the maxilla or mandible
- at least one neighboring natural tooth to the defect site(s)
- signed informed consent

At the day of surgery, patients were randomly assigned to receive one out of two treatment modalities for the reconstruction of the horizontal ridge deficiencies:

i) a DBBM block (Bio-Oss Spongiosa Block®, Geistlich Pharma AG, Wolhusen, Switzerland) loaded with rh-BMP-2 (InductOs®, Medtronic BioPharma, Neuchâtel, Switzerland) (test). InductOs® is commercially available as an 8 ml dose with a concentration of 1.5 mg/ml. It is produced in chinese hamster ovary (CHO) cells, the product is registered for vertebral surgeries only in Switzerland. An in vitro investigation revealed that in combination with this carrier, the concentration of rhBMP-2 is reduced by 30% up to day 5 (data on file).

ii) an autogenous bone block combined with DBBM particles (Bio-Oss Granules®, Geistlich Pharma AG, Wolhusen, Switzerland) (control).

Surgical procedure

Prior to the start of the surgery, patients rinsed with 0.2% of chlorhexidine (Meridol® Perio Chlorhexidin Lösung 0.2%, GABA, Switzerland), received analgesic and anti-inflammatory

medications (Ponstan®, Parke-Davis, Baar, Switzerland) and a first dose of penicillin (3g) (Clamoxyl®, SmithKline Beecham AG, Thörishaus, Switzerland). The area/areas intended for surgery were carefully anaesthetized (Ultracain® D-S, Hoechst-Pharma AG, Zurich, Switzerland) (Figures 1a + 2a).

Recipient site preparation: A paracrestal incision placing the line of incision towards the palatal aspect of the ridge was applied. Oblique releasing incisions were used to allow for a wide flap basis as well as sufficient access to the defective ridge area. Any soft tissues remaining on the crest were meticulously removed and the ridge width was measured. The cortical bone plate was perforated at numerous locations.

Donor site preparation (control only): Depending on the size of the ridge defect (recipient site) and the donor site anatomy, the blocks were harvested from the symphysis or the retromolar area. A mucoperiosteal flap was elevated at the donor site, followed by preparation with a fissure bur or a piezo device and careful block graft mobilization (von Arx and Buser, 2006)(Figure 2b).

Ridge augmentation at recipient site: In the test group, rhBMP-2 was re-suspended in sterile ultra-purified water according to the manufacturers protocol. The DBBM block was then moistened for 15 minutes with 1.2 ml rhBMP-2 (InductOs®, rhBMP-2 concentration 1.5 mg/ml), rendering a final concentration of 1.8 mg growth factor per ccm of DBBM block (Figure 1b). The xenogeneic block was shaped with a blade and adapted to the defect. In the control group, the blocks were adapted to the defect site morphology. With a small drill, holes for fixation (GBR-System, Institute Straumann AG, Basel, Switzerland) were prepared and the bone blocks were immobilized with one or two screws (Figure 2c). Subsequently, a layer of xenogeneic bone particles was applied to cover the autogenous bone and to fill up voids in both groups.

The obtained ridge width was again measured before application of the membrane. In both groups, the collagen membrane was trimmed to extend the augmented area 2-3 mm onto the intact bony borders of the defect. The membrane was fixated using resorbable fixation pins (ZorbTac®, Imtec, 3MEspe, Oberursel, Germany). Tension free wound closure was obtained through releasing incisions in the periosteum. A horizontal mattress suture and further single interrupted sutures (Gore-tex® 5-0 sutures, W.L. Gore & Associates, Flagstaff, AZ, USA) were placed intending a primary wound closure in both groups.

All patients received analgesic and anti-inflammatory medications (Ponstan®), and were instructed to rinse with chlorhexidine (Meridol® Perio Chlorhexidin Lösung 0.2%). A second dose of penicillin (Clamoxyl®) (1.5g) was prescribed 6 hours after the first dose. Subsquently, penicillin was given for 7 consecutive days (2.25g per day). Temporary removable partial dentures were carefully checked and adapted if necessary to avoid trauma to the surgical area. Between 7 and 9 days following augmentation surgery, all sutures were removed.

Re-entry at 4 months

Four months following ridge augmentation, re-entry surgery and implant placement was performed. After rinsing with chlorhexidine (Meridol® Perio Chlorhexidin Lösung 0.2%) and application of local anaesthetics (Ultracain® D-S), flaps were raised in order to visualize the augmented ridge (Figure 1d + 2d). A hard tissue biopsy was obtained in the prospective implant position by means of a trephine bur with an inner diameter of 1.8mm (Figure 3a). Subsequently, implants were placed according to the manufacturer's instruction and in a prosthetically ideal position (Figure 1e + 2e). Additional GBR procedures were performed in case of dehiscence or fenestration defects at the implants. Flaps were then adapted to allow either for a transmucosal or for a submerged healing of the implant (data not reported here).

Processing of histologic samples

The specimens obtained at the re-entry four months after augmentation were fixed with 4% formalin for at least 48 hours. Specimens within the trephine bur were carefully removed, rinsed in running tap water, trimmed and dehydrated in a graded series of increasing ethanol concentrations. Thereafter, they were embedded in methylmethacrylate without being decalcified. Tissue blocks were cut into 200-µm-thick vertical sections using a slow-speed diamond saw (VARICUT® VC-50; Leco, Munich, Germany). The sections were polished to a final thickness of 80–100 µm (Knuth-Rotor-3; Struers, Rødovre/Copenhagen, Denmark), and surface-stained with toluidine blue.

Measurements

In patients with more than one prospective implant site, the most mesial site was chosen for analysis. In case there were two most mesial implant sites, one was chosen randomly. The respective time-points of all measurements are shown in figure 4.

Clinical measurements

The ridge width was measured by means of a caliper to assess the oro-facial bone width to the nearest millimeter at the prospective implant site after flap elevation, after augmentation and at 4 months. Furthermore, plaque index (PI), probing depth (PD), bleeding on probing (BoP) and the width of the keratinized mucosa (KM) at neighboring teeth were assessed prior to augmentation surgery and at 4 months. The status of the soft tissues was rated as normal (1), red (2), swollen (3) or dehiscence (4) on a scale from 1 to 4 at suture removal and at 4 months. Anamnestic information in terms of sensitivity were reported at suture removal and at 4 months and were rated as normal (1) or disturbed/not present (0).

Patient reported outcome measures (PROMs)

A total of seven questions were evaluated at suture removal using a visual analogue scale (VAS score; VAS 0-100, 100 reflecting the highest morbidity). Pain during surgery, pain and swelling in the week following ridge augmentation until suture removal were assessed for the recipient and the donor site (control only). Patients were further asked about their willingness to repeat the treatment. In addition, the use of pain medication and the number of days pain medication was taken were reported at the same time-point.

Histomorphometric assessment

The histomorphometric analysis was performed by means of a software program (LAS V4.3, Leica Microsystems, Wetzlar, Germany). Within the selected region of interest (ROI), the percentage of bone, bone substitute material, soft tissue and background were analyzed.

Statistical analysis

The data was collected in Excel (Microsoft Corporation, Redmond, Washington, USA) and statistical analysis was performed with SAS 9.4 (SAS Corp., Cary NC. USA). Mean, standard deviations (SD), medians, quartiles and min/max are derived for continuous variables and counts for categorical data. Intergroup comparisons were tested by a two-sided Wilcoxon-Mann-Whitney test because of the small sample size and the non-normality of the data and intragroup comparisons were performed with Wilcoxon-signed rank test for continuous variables. All categorical variables were tested with Chi-squared tests or Fisher's exact test. The primary endpoint is the clinically evaluated ridge width. In order to allow commenting on the possible equivalence of the two groups, the 90% confidence intervals were provided in addition. The significance level was set at 5%. No correction for the multiple testing for the secondary endpoints is applied. Possible confounding factors, e.g. center effect, were investigated for the primary endpoint with nonparametric ANOVA models.

Results

In one patient included, an autogenous bone block was exposed 6 days after surgery. The block was removed after 21 days, since antiseptic treatment was not successful. As the patient refused to repeat the intervention, he was excluded from the study and was replaced by an additional patient according to the study protocol, also receiving an autogenous bone block. The subsequent 24 patients were consecutively treated as follows: 14 patients at the Clinic for Fixed and Removable Prosthodontics and Dental Material Science, University of Zurich, Zurich, Switzerland and 10 patients at the Department of Oral Surgery and Radiology, School of Dentistry, Medical University Graz, Graz, Austria. The median age amounted 58.0 years (Q1 (first quartile) = 44.0; Q3 (third quartile) = 66.0) in the test group and 46.5 years (Q1 = 34.0; Q3 = 61.5) in the control group. The test group consisted of 66% males and the control group consisted of 50% males.

Prior to bone augmentation, the median ridge width amounted to 4.0 mm (Q1 = 2.0; Q3 = 4.0) in the test group and to 2.0 mm (Q1 = 2.0; Q3 = 3.0) in the control group. Due to the surgical intervention, the median values increased to 7.0 mm (Q1 = 6.0; Q3 = 9.0) in the test group and 7.0 mm (Q1 = 6.0; Q3 = 8.0) in the control group postoperatively. At re-entry at four months, the median ridge width amounted to 7.0 mm (Q1 = 6.0; Q3 = 8.0) for test and 7.0 mm (Q1 = 6.0; Q3 = 8.0) for control. The intergroup comparison revealed no statistically significant differences of the medians, except for the preoperative ridge width that exhibited a borderline significance ($p=0.0581$). The intragroup comparison over time showed a statistically significant increase due to the surgical intervention ($p=0.002$ for test and control), but the changes during the healing period from postoperative to four months was not statistically significant ($p>0.2422$). The difference between the two centers was not statistically significant for both groups and all three time-points ($p>0.1612$). All descriptive measures are given in table 1 and ridge width measurements of every single patient are given in the appendix.

The corresponding 90% confidence intervals amounted to [-2, 0] prior to the augmentation, [3, 5] postoperatively and [-2, 0] at 4 months.

The clinical parameters did not demonstrate to have statistically significantly different group medians ($p>0.1855$). The median BoP measured 0.0 % (Q1 = 0.0; Q3 = 16.7, test) and 0.0 % (Q1 = 0.0; Q3 = 12.5, control) at baseline and 0.0 % (Q1 = 0.0; Q3 = 20.8, test) and 12.5 % (Q1 = 0.0; Q3 = 33.3, control) at 4 months. The amount of KM measured 3.8 mm (Q1 = 3.0; Q3 = 4.0, test) and 3.0 mm (Q1 = 2.0; Q3 = 4.0, control) at baseline and 3.5 mm (Q1 = 3.0; Q3 = 4.0, test) and 3.0 mm (Q1 = 2.0; Q3 = 3.8, control) at 4 months. The median soft tissue condition was rated 3.0 (Q1 = 1.8; Q3 = 3.0) in the test group and 2.0 (Q1 = 1.0; Q3 = 3.0) in the control group at suture removal and dropped to 1 (Q1 = 1.0; Q3 = 1.0 for both groups) for all patients at 4 months. The two groups did not show statistically significant different medians ($p>0.4003$). The intraoral sensitivity was rated normal in 58 % (SD (standard deviation) = 49) for both groups at suture removal, raised to 91 % (SD = 29) in the test group and dropped to 50 % (SD = 50) in the control group at 4 months. All inter- and intragroup comparisons were not statistically significantly different. There was, however, a borderline effect between the groups at 4 months ($p=0.0635$). The extraoral sensitivity was intact in 58 % (SD = 49) in the test group and 67 % (SD = 47) in the control group at suture removal, raised to 92 % (SD = 28) in the test group and dropped to 50 % (SD = 50) in the control group at 4 months. All inter- and intragroup comparisons were not statistically significantly different. There was, again, a borderline effect between the groups at 4 months ($p=0.0686$).

All patients except one had taken pain killer medication post augmentation surgery. The median number of days pain medication was taken was 3.0 (Q1 = 1.0; Q3 = 5.0) in the test group and 4.0 (Q1 = 2.0; Q3 = 6.0) in the control group ($p=0.1414$). The results of the questionnaires are presented in figure 5. The obtained data did not differ statistically significantly between the groups except for pain at the recipient site during surgery, which amounted 7.0 (Q1 = 0.0; Q3 = 20.0, test) compared to 30.0 (Q1 = 10.0; Q3 = 5.0, control) ($p=0.0236$).

Four months following augmentation surgery, in all 24 patients, implant placement was possible and hard tissue biopsies were harvested. The biopsies in the test group contained a median amount of 29.8 % (Q1 = 18.4; Q3 = 40.5) bone, of 9.6 % (Q1 = 3.3; Q3 = 31.3) bone substitute, of 31.5 % (Q1 = 12.4; Q3 = 44.9) soft tissues and of 15.6 % (Q1 = 4.3; Q3 = 28.2) background. The control group consisted of 75.8 % (Q1 = 68.2; Q3 = 87.0) bone, of 0.0 % (Q1 = 0.0; Q3 = 0.0) bone substitute, of 7.8 % (Q1 = 0.9; Q3 = 12.4) soft tissues and of 14.4 % (Q1 = 6.9; Q3 = 21.3) background. The differences in the amount of bone, bone substitute and soft tissues were statistically highly significant ($p<0.0043$) (Figure 3b+c).

All descriptive results are given in tables 1 and 2.

Discussion

The present two-center randomized controlled trial demonstrated that i) both treatment modalities (rhBMP-2 loaded on a xenogeneic block graft and the autogenous bone block) rendered sufficient ridge width to place dental implants, ii) between post surgery and the 4-month follow-up, less than 0.6mm of ridge width was lost, iii) PROMs were not statistically significantly different from the control group for the majority of the outcome measures and, iv) the tissue obtained through biopsies at 4 months consisted of 50% (test) and 75% (control) mineralized tissue.

A plethora of preclinical and clinical studies evaluated rhBMP-2 with various combinations of scaffold materials (Agrawal and Sinha, 2016). The collagen sponge, which is probably the first and most frequently investigated carrier, appears to lack space-maintenance for primary augmentation without the addition of a space-maintaining device (Barboza et al., 2000). Consequently, promising results were reported for combinations of a collagen sponge loaded with rhBMP-2 with a titanium mesh (de Freitas et al., 2016, Ribeiro Filho et al., 2015, de Freitas et al., 2013). A combination of anorganic bovine bone loaded with rhBMP-2 and a titanium mesh lead to comparable results, based on a retrospective case series (Butura and Galindo, 2014). Apart from space-maintaining membranes, bone substitute materials might serve as form-stable carrier materials. More than a decade ago, rhBMP-2 was combined with a xenogeneic bone substitute material for localized bone regeneration at buccal dehiscence defects. That clinical study demonstrated more favorable results when rhBMP-2 was added to xenogeneic granules compared to a control group without the growth factor (Jung et al., 2003). These data were later supported by a series of preclinical studies, all demonstrating the high potential of this combination for localized bone regeneration (Schwarz et al., 2009, Gruber et al., 2014, Yon et al., 2015, Thoma et al., 2015). Due to the size of the defect and thereby a further need of stability of the augmentation in the present study, the DBBM Block was used. These blocks have shown a rather poor ingrowth of bone in a preclinical study, but appeared to be efficient in keeping the augmented dimension (Benic et al., 2016). Apart from this, a clinical case series

demonstrated successful primary augmentation using the same DBBM block material. As a disadvantage, that protocol required a relatively long healing time (Hammerle et al., 2008). Predominantly the latter study indicated that such DBBM blocks can indeed serve for primary augmentation. In order to reduce the healing time, DBBM was combined with the growth factor (rhBMP-2).

Narrow ridges presenting an insufficient width to place dental implants are common in daily practice. The use of autogenous tissue is considered to be the gold standard to regenerate the missing volume and to allow for dental implant placement. The combined use with DBBM particles in the control group can be seen as a confounder on one hand, but the beneficial effect in terms of a slower graft resorption is documented (Maiorana et al., 2005, Wiltfang et al., 2014, Cordaro et al., 2011). Thus, the test group was compared with the best treatment modality available.

From a clinical point of view, the ability to place dental implants following a healing period after primary bone augmentation is considered as the main goal of the therapy (Ribeiro Filho et al., 2015, Marx et al., 2013, Butura and Galindo, 2014, Misch et al., 2015). This was underlined by the outcomes of the present study, demonstrating that both treatment modalities were successful and allowed placing dental implants in all sites (except in one patient where an autogenous bone block failed). When comparing economic aspects, the test group can be considered advantageous in terms of surgical efforts as there is no harvesting procedure. In contrast, there are more expenses for materials i.e. the DBBM block and the growth factor. An 8ml dose costs 4500 swiss francs, however, 2ml were enough to moisten the block and the volume of one block was sufficient to augment up to 4 neighboring sites.

None of the two groups was more favorable based on ridge dimensions being similar at the day of augmentation (post surgery) and at 4 months. The overall increase in ridge width amounted to 4mm (test) and 5mm (control). These data are in line with previous clinical studies on primary bone augmentation using autogenous bone blocks or rhBMP-2 in combination with titanium-reinforced porous polyethylene containments (Hart and Bowles, 2012, Monje et al., 2015,

Cordaro et al., 2002). The graft resorption is generally reported to be higher for autogenous bone compared to DBBM (Gultekin et al., 2016, Jensen et al., 2006). In the current study, the resorption rate (ridge width) during the healing phase was relatively low. This might be due to the coverage with DBBM particles of the autogenous graft (Wiltfang et al., 2014, Cordaro et al., 2011) as well as due to the relatively short observation period. The amount of resorption for autogenous grafts is highly variable in the literature and might result in a loss between 5.5-22% (Cordaro et al., 2011) but up to 60% (Widmark et al., 1997).

Apart from the main objective to regenerate missing volume, patients' demands increased in the past for therapeutic options associated with less morbidity and less complications. PROMs are frequently used to assess patient morbidity using various scoring systems and questionnaires. In the present study, patient-reported outcome measures included: questionnaires using a visual analogue scale (VAS) to assess pain during surgery and postoperative pain, the reported number of days pain medication was used and clinical measurements to evaluate intra- and extraoral sensitivity. The test group without a second surgical site demonstrated less pain during surgery at the recipient site, a lower number of days that pain medication was taken (2.8 days for test vs. 4.4 days for control) and more sites with an intact intraoral (91% for test vs. 50% for control) and extraoral (92% vs. 50%) sensitivity at 4 months. One has to bear in mind, however, that the majority of the assessed PROMs were not significantly different between the two treatment modalities. In terms of swelling, comparable results were reported in both groups. This is quite surprising as previous studies reported a considerable swelling after the use of rhBMP-2 (Marx et al., 2013, Edmunds et al., 2014). The assessment of PROMs to detect differences between treatment modalities is difficult to achieve for any surgical intervention in the oral cavity. Unfortunately, in the control group, pain and swelling was assessed separately for donor and recipient sites. Due to this fact, no overall pain and swelling rates were possible to calculate, probably resulting in only minor differences between the groups. Previous studies assessing surgical interventions with (autogenous tissue) or without (substitute material) a second surgical site reported similar difficulties to demonstrate significant differences between two or more treatment modalities (McGuire and Nunn, 2005). It remains questionable if the

patients were able to locate the recipient site and distinguish it from the donor site. In addition, there might be an upper limit in terms of how much pain is perceived in the oral cavity. The addition of a further surgical site increased the overall pain perception, but probably not enough to detect substantial differences between the two groups. Further parameters that might have influenced the unexpectedly low differences were: high standard deviations, two centers involved, relatively small area that underwent primary bone augmentation (1-4 sites).

At the day of implant placement, core biopsies were harvested and the regenerated tissues were analyzed. For the autogenous group, a high amount of mineralized tissue (75%) was found. For the combination of rhBMP-2 and the xenogeneic block graft, the amount of mineralized tissue was significantly lower (50%). In a comparable study, biopsies were taken at 6 months compared to present biopsies harvested at 4 months (de Freitas et al., 2016). The amount of mineralized tissue was similar for the autogenous blocks compared with a collagen sponge loaded with rhBMP-2 under a titanium mesh, again proving the regenerative potential of the growth factor. Moreover, the amount of mineralized tissue obtained for rhBMP-2 combined with DBBM was comparable to previous clinical data on lateral ridge augmentation, with core biopsies taken at the buccal aspect and a rate of mineralized tissue reported to range between 40 and 50% (Jung et al., 2003).

The outcomes of the present study and the respective translation into daily practice are to some extent limited by i) a slight imbalance at baseline with larger defects in the control group (borderline significance), ii) difficulties for patients to distinguish between the recipient and donor sites when PROMs were analyzed, iii) a limited number of patients (exploratory study without power analysis), iv) a short observation period of 4 months and, v) by the fact that the xenogeneic block graft (almost worldwide) and rhBMP-2 (in some countries as a combination with a resorbable collagen sponge; e.g. USA and Canada) are commercially available, but not worldwide (rhBMP-2) and not as a combination product.

Conclusions

Both treatment modalities were successful in regenerating bone and increasing the ridge width in order to allow for dental implant placement at 4 months. PROMs did, in general, not reveal any significant differences between the groups except for pain during surgery at the recipient site (in favor of the test group). Histologically, a higher amount of mineralized tissue was observed for the control group at 4 months.

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Figure legend

Figure 1 a-e. A series of clinical pictures of a patient treated in the test group: before flap elevation (a), moistening of the xenogeneic block with rhBMP-II (b), adaption of the block at the surgical site (c), reentry at 4 months (d), implant placement at 4 months (e)

Figure 2 a-e. A series of clinical pictures of a patient treated in the control group: before flap elevation (a), harvesting of an autologous block in the retromolar area (b), adaption of the block at the surgical site (c), reentry at 4 months (d), implant placement at 4 months (e)

Figure 3 a-c. Harvesting procedure of a hard tissue biopsy in the prospective implant bed at the reentry intervention at 4 months (a), representative histologic sample of the test group, toluidine blue staining (b), representative histologic sample of the control group, toluidine blue staining (c)

Figure 4. Timeline containing all time-points with measurements involved

Figure 5. Patient reported outcome measures from a questionnaire with 7 questions answered on a visual analogue scale with a score from 0-100, with 100 reflecting the highest morbidity. The data is presented as a mean with standard deviation. Pain during surgery at the recipient site was statistically significantly different ($p<0.05$). The willingness to repeat the treatment was generally high. Control = autologous bone block; test = xenogeneic block with rhBMP-II

Table 1. Descriptive results part 1: control = autologous bone block; test = xenogeneic block with rhBMP-II, N = number; SD = standard deviation; Min = minimum; Q1 = 25% quartile; Q3 = 75% quartile; Max = maximum ; P Wilcoxon/Chi-square test = p-values of the according statistical test

Table 2. Descriptive results part 2: VAS = visual analogue scale; control = autologous bone block; test = xenogeneic block with rhBMP-II, N = number; SD = standard deviation; Min = minimum; Q1 = 25% quartile; Q3 = 75% quartile; Max = maximum ; P Wilcoxon/Chi-square test = p-values of the according statistical test

Appendix table 1. Ridge width measurements listed for every single patient containing all evaluated time-points, assorted by group. Control = autologous bone block; test = xenogeneic block with rhBMP-II; ZRH = University of Zurich, Zurich, Switzerland; GRZ = Medical University Graz, Graz, Austria